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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/656,811	06/03/96	BARTSCH	D 50865/JPW/JM

EXAMINER	
18N2/1110	

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ART UNIT	PAPER NUMBER
1817	10

DATE MAILED: 11/10/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/25/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-27 is/are pending in the application.

Of the above, claim(s) 7-14, 23-27 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-6, 15-22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-6 and 15-22 as reading on a compound that interferes with binding and small molecule (claims 4, 19) in Paper No. 9 filed 7/25/97 is acknowledged. The traversal is on the ground(s) that (a) Applicant asserts that 35 U.S.C. 121 demands the inventions be examined together due to an asserted "relatedness" and (b) MPEP 803 is asserted to indicate an undue search burden which demands the inventions be examined together. This is not found persuasive because (a) MPEP states that for restriction the invention must be independent or distinct (page 800-3, right column, rev 2, July 1996) and "distinct" is defined as including related subject matters that are patentable over one another (left column, same page) and (b) the restriction requirement was not based solely upon search burden and Applicant has not responded to the cited basis for restriction (e.g. 806.05(h)).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2 and 17 of Group I are withdrawn from consideration as non-elected. Claims 4 and 19 are examined as reading on a small molecule as per Paper No. 9. Claims 1, 3-6, 15-16 and 18-22 are examined.

Claim Rejections - 35 U.S.C. § 112

3. Claims 1, 3-6, 15-16 and 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitations of "enhance", "repressed", "derepressed", "associated", "interfere"and "interfering" are vague and indefinite.

i. The terms "enhance", "repressed", "derepressed" in claim 1 are relative terms which renders the claims indefinite. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

ii. The term "associated" (claim 1, 5, 15) is unclear because it does not sufficiently describe how a protein or DNA as recited is related to cAMP-responsive gene expression, and therefore one of skill in the art would not know what is encompassed by the claim. For example, the protein or DNA "associated" with cAMP-responsive gene expression may be indirectly related to cAMP-responsive gene expression or a general housekeeping protein or DNA which affects all gene expression.

iii. The terms "interfere" and "interfering" in claims 1 and 15 do not define how binding of the recited protein or DNA is affected by the compound, and therefore one of skill in the art would not know what is encompassed by the claim.

b. The recitations of "binding of the protein or the DNA so as to..." in claim 1, line 8 and claim 15, lines 7-8 are vague and indefinite because the claims do not recite to what the protein or DNA binds, therefore one of skill in the art would not know what is encompassed by the claims.

c. The recitations of "small molecule" in claim 4 and 19 are vague and indefinite because "small" is a relative terms which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

d. The recitations of "such binding" in claims 1 and 15 are vague and indefinite because it is not clear what is encompassed by "such binding". For example, "such binding" reads not only upon the binding recited previously in the claims, but also encompasses similar (e.g. not the same) binding.

e. The recitations of "treating" and "treat" in claim 15 are vague and indefinite because it is unknown what constitutes treating or treatment and therefore one of skill in the art would not know what is encompassed by the claim. For example, the outcome of treatment is unknown (e.g. complete curing of defect, partial alleviation of symptoms, etc.).

f. The recitations of "gene bombardment" in claims 6 and 22 are vague and indefinite because "gene bombardment" is a laboratory designation and as such may not be standard to all practioners in the art. It is suggested that "gene bombardment" be accompanied by descriptive nomenclature.

g. The recitations of "defect" in claim 15 are vague and indefinite because it is not known what is encompassed by the term. For example, "defect" could refer to a degree of memory loss, the inability to create a memory, incomplete or incorrect memory building, or other.

h. The Markush grouping of claim 16 is improper. The listing of conditions comprises conditions which are not themselves not memory defects. For example: Alzheimer's Disease is not a memory defect as recited, but is a condition which has as a symptom a memory defect; ischemia is not a memory defect per se, etc..

i. The recitations of "comprises" in claims 20 and 5 are vague and indefinite because it is unclear how a protein can comprise more than a whole functional protein such as those recited in the claims.

j. Claims 5, 6, 16, 20, 20, 22 are indefinite in the use of improper Markush language, e.g. "from the group comprising", as this language does not clearly define the members of the group. Proper Markush language should recite either "selected from the group consisting of A, B and C" or "selected from A, B or C".

k. The recitation of "capable of altering the phosphorylation" in claims 3 and 18 are vague because it is not known if said altering is necessary to the method, and therefore is not a positive limitation in the claim.

l. The recitations of ApC/EBP and c/EBPβ are vague and indefinite because ApC/EBP and c/EBPβ are laboratory designations and as such may not be standard to all practioners in the art. It is suggested that "ApC/EBP and c/EBPβ" be accompanied by descriptive nomenclature or SEQ ID No.

4. Claims 1, 3-6, 15-16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of enhancing long-term memory in a subject which has repressed cAMP-responsive gene expression due to binding of a protein or DNA (associated with cAMP-responsive gene expression) to a CREB-2 by administration of a compound.

a. However, claim 1 does not recite that the subject's cAMP-responsive gene expression, repressed or otherwise, correlates to memory function. Further, the specification is insufficient to direct one of skill in the art to the broadly claimed "subject" of independent claims 1 and 15 in which CREB-2 mediated cAMP-responsive gene expression does correlate with long-term memory, and wherein perturbation of the subject's cAMP-responsive gene expression will effect long-term memory in a predictable manner. The state of the art does not support the claimed correlation between the broadly claimed subject's long-term memory with cAMP-responsive gene expression, and in particular CREB-2 mediated cAMP-responsive gene expression.

For example, it is clear from the specification and the claims that Applicant intends the claims to encompass human subjects with normal memory function and human subjects with memory defects. Though the specification exemplifies changes in long term facilitation in Aplysia (as measured by gill withdrawal reflex coupled with a 5-HT pulse), long term facilitation in

Aplysia is not predictive of more complex memory function in, for example, primates, which are likely to involve multiple systems in the memory process (e.g. Cooper et al (1991) "The Neurobiological Basis of Neuropharmacology, sixth edition" Oxford University Press, page 443-445, in particular 443 lines 12-16). In fact, long term potentiation may not be a completely predictive model of the learning or memory processes in Aplysia (e.g. Glanzman, Trends Neurosci. (1995) 18 pages 30-36). Physiologic and anatomic differences between the CNS of Aplysia and humans further lower the predictive value of the invertebrate model in regard to the broadly claimed subject population. It is also noted that Applicant has claimed use of the method in subjects with widely divergent memory defects due to such as conditions as Alzheimer's Disease, Parkinson's Disease, head trauma; such conditions have completely different etiologies. One of skill in the art would not predict that the underlying cause for memory defect is the same in these conditions and therefore would not predict efficacious treatment of each to comprise the same methodology. (See for example, Cooper et al (1991) "The Neurobiological Basis of Neuropharmacology, sixth edition" Oxford University Press, page 443-445, in particular 444-445, bridging paragraph). Finally, Applicant has not provided a means of identifying suitable subjects commensurate in scope with the claims, wherein said method can be accomplished with a reasonable expectation of success, nor has Applicant provided a means commensurate in scope with the claimed subject to assay either the molecular events claimed or the cognitive effect of the method.

Therefore, the unpredictability of the correlation between the broadly claimed subject's long-term memory with cAMP-responsive gene expression, and in particular CREB-2 mediated cAMP-responsive gene expression, in contrast to single working example provided in the specification combined with the paucity of direction or guidance presented in the specification and the state of the prior art; one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

b. Additionally, the molecular mechanism claimed, both in relation to memory function and on its own, is sufficiently unpredictable that its components render the claims non-enabled. The recitation of "cAMP-responsive gene expression" encompasses a myriad of transcriptional events because cAMP is a ubiquitous second messenger. One of skill in the art would not predict that any particular cAMP-responsive transcriptional event would result in the claimed effect on memory. In the absence of guidance as to what gene products will predictably effect memory in the broadly claimed subject population, and in the absence of an assay which would identify such gene products commensurate in scope with the claimed subject population and effect, the identification of appropriate transcriptional events within the broadly claimed cAMP-responsive gene expression would require undue experimentation. Likewise, the identification of a CREB-2 sensitive protein or DNA which is associated with cAMP-responsive gene expression and predictably effects memory function is unpredictable. Though assays for CREB-2 sensitivity and appropriate promoter regions for in vitro transcriptional assays are known, the breadth conferred by the recitation of "a protein or a DNA" leaves open the universe

of possible proteins and DNA sequences, which would require undue trial and error experimentation to narrow to the small number of functional embodiments.

c. In regard to the broadly claimed compound which interferes with binding, the instant claims have been limited to read upon a small molecule. However, "small molecule" can encompass any molecule which may be considered small, including inorganics as well as peptides, etc. In contrast, the specification exemplifies only an antibody with the recited properties of binding interference and effect. It is noted that practioners in the art do not consider antibodies to be small peptides, but large complex structures, therefore, it is deemed the specification provides no working examples of the claimed compound. Generation of an antibody with the recited functional (ability to interfere with binding) and therapeutic characteristics is unpredictable, identification of non-antibody compounds which are encompassed by the claims even more so. Applicant has not provided guidance as to what particular compounds of the broadly claimed compounds may function in the claimed method.

Further, it is noted that dependent claims 3 and 18 are drawn to the compound's ability to alter phosphorylation of CREB-2. It is known that CREBs are phosphorylated in multiple locations and that their activity depends upon the particular pattern of phosphorylation. As the particular phosphorylation pattern which would be favorable to the recited methods is not known, one of skill in the art would need to determine how phosphorylation correlates with functioning in the instant method without direction from the instant specification or the state of the art.

Therefore, the unpredictability associated with identification of small molecular compounds with the recited properties, in contrast to the insufficient direction, guidance or working examples commensurate in scope with the claimed compound presented in the specification and the state of the prior art; one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3-6, 15-16 and 18-22 are rejected under 35 U.S.C. 102(a or b) as being anticipated by Yin et al Cell 81 (1995) pages 107-115.

Yin et al teach administration of a heat shock activated CREBP-2 (hs-d-CREB2-a), a compound that interferes with CRE binding, to Drosophila via transgenic techniques. The reference teaches that activation of the mutant gene increases long term memory.

7. Claims 1, 3-6, 15-16 and 18-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Bartsch et al, Cell 83(6) 1995 pages 979-992.

Bartsch et al teach the injection of anti-ApCREB2 antibodies into Aplysia sensory neurons, resulting in increased long term facilitation.

Conclusion

8. Any inquiry concerning this communication should be directed to Heather Bakalyar at telephone number (703)305-7143.

The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached on (703) 308-4310. The official fax phone number for this Group is (703)308-4242.

9. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group 1800 receptionist whose telephone number is (703)308-0196.

Heather Bakalyar, Ph.D.

10/24/97

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800